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Endogenous Type-I Interferon Activity is not Associated with Depression or Fatigue in Systemic Lupus Erythematosus

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Abstract

Patients with systemic lupus erythematosus (SLE) often suffer from depression and fatigue in addition to the physical manifestations of the autoimmune disease. Elevated production of type-I interferons (IFN-I) has been found in lupus patients and IFN-I can precipitate a variety of neuropsychiatric side effects. This study was conducted to evaluate the relationship between dysregulated IFN-I production and the presence of depression or fatigue in lupus patients. Through cross-sectional and longitudinal analysis we found no significant correlation between abnormal IFN-I levels (as measured by peripheral blood expression of IFN-I-stimulated genes) and neuropsychiatric manifestations. Elevation of endogenous serum IFN-I levels is unlikely to account for the depression and fatigue associated with SLE.

Keywords

Systemic lupus erythematosus; depression; fatigue; type I interferon

1. Introduction

Systemic lupus erythematosus (SLE) is a debilitating condition affecting multiple organ systems including the skin, kidneys, liver, heart, lungs, and nervous system (Reeves et al., 2004). In addition to the autoimmune manifestations, more than half of patients with SLE suffer from depression and fatigue (Krupp et al., 1990; Shortall et al., 1995). Interestingly, although SLE is characterized by cycles of disease flare and remission, the prevalence of depression and fatigue is not adequately explained by disease activity or other disease related variables (Gladman et al., 1996; Jump et al., 2005; Wang et al., 1998). It remains uncertain whether these neuropsychiatric symptoms are due to the burden of having a chronic illness or other factors.

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Recent studies suggest that type-I interferons (IFN-I) may play an essential role in the etiology of SLE (Lee and Reeves, 2006). Several groups have demonstrated that more than half of SLE patients exhibit high serum levels of IFN-I and over-express a group of IFN-I-stimulated genes (ISGs) in their peripheral blood cells (Baechler et al., 2003; Bennett et al., 2003). The presence of this interferon signature is associated with active disease, the presence of certain autoantibodies, and an increased incidence of renal involvement (Feng et al., 2006; Kirou et al., 2005; Zhuang et al., 2005).

IFN-I are a family of anti-viral cytokines that includes IFN- β and all subtypes of IFN- α . Produced endogenously by the body in response to viral infection, IFN-I possess a number of immunostimulatory and anti-proliferative functions (Pestka et al., 2004). These properties provide a rationale for using recombinant IFN-I to treat viral infection (e.g. hepatitis C) and certain malignancies (e.g. carcinoid syndrome) (Veenhof et al., 1992; Weimar et al., 1980). Interestingly, IFN-I treatment also can modulate the levels of other cytokines, chemokines and neurotransmitters within the CNS (Raison et al., 2009a). Therapeutic use of IFN- α induces neuropsychiatric side effects including psychosis, fatigue, and depression in patients without any history of psychiatric findings (Dieperink et al., 2000; Schaefer et al., 2002). Due to the increased risk for suicidal ideation, IFN- α therapy is contraindicated in patients with depression (Dieperink et al., 2004; Janssen et al., 1994).

Based on the psychiatric side effects of IFN-I therapy, we hypothesized that elevated serum levels of IFN-I might contribute to the neuropsychiatric manifestations of SLE. In this study, we evaluated the relationship between dysregulated IFN-I production and the presence of depression or fatigue in lupus patients.

2. Materials and Methods

Study Subjects

Fifty-eight patients meeting the American College of Rheumatology classification criteria for SLE (Tan et al., 1982) were recruited from the University of Florida Center for Autoimmune Diseases clinic. This study was approved by the University of Florida Institutional Review Board and all participants provided informed consent prior to participation in the study. Each patient was given three sets of questionnaires to complete and peripheral blood was obtained from each patient to assess the expression of ISGs, a surrogate marker of serum IFN levels. Peripheral blood was also obtained from twenty healthy volunteers who served as a control group for ISG expression analysis (see below). The control group was similar in age and race distribution compared to the patient group (Table 1). At the time of data collection, 49 of the 58 patients were receiving treatment with corticosteroids, antimalarials, and/or cytotoxic medications. The number of patients receiving each class of medications is provided in Table 1. In cross-sectional-analysis, retrospective data on the usage of these medications were not apparently associated with changes in ISG expression or the levels of depression or fatigue (Supplemental Table 1).

Measurement of depression

Depression was measured using the Beck Depression Inventory (BDI) (Beck et al., 1961). This 21 question survey yields a score range from 0–63. A score of 0–9 is considered minimally depressed, 10–18 represents mild to moderate depression, 19–29 indicates moderate to severe depression, and > 29 is suggestive of severe depression. BDI is an accurate measure of depression in individuals with lupus (Iverson et al., 2001).

Measurement of fatigue

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) (Smets et al., 1995). The MFI consists of 20 questions divided into 5 different areas of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Participants were provided with statements regarding their feelings and a score ranging from 0–4 was given based on how much they agree or disagree with each statement. A total score ranging from 4–20 was calculated for each category upon combining the individual scores from the questions pertaining to each dimension of fatigue.

Visual analog scales

Visual Analog Scales (VAS) were administered as an additional measure of depression and fatigue. The levels of pain, anxiety, and anger were also assessed using this format as described previously (Jump et al., 2005). For each item, participants were asked to draw a vertical line on a 100 millimeter horizontal line placed between “None” on the left and “Most Possible” to the right based on their feelings on the particular day and not on average. Results were determined by measuring the distance (in millimeters) of the vertical line from the left end of the 100 mm line.

Interferon-stimulated gene expression

Peripheral blood expression of mRNA for ISGs was measured by quantitative real-time polymerase chain reaction (Q-PCR) as described (Lee et al., 2007; Zhuang et al., 2005). This method quantifies the activity of all IFN-I subtypes including IFN- α and IFN- β . Briefly, blood was collected in Paxgene tubes (Qiagen, Valencia, CA) following the completion of the questionnaires. RNA isolation was performed using the PAXgene Blood RNA kit (Qiagen) following the manufacturer’s protocol. Complementary DNA (cDNA) was synthesized using a Superscript II First-Strand Synthesis Kit (Invitrogen, Carlsbad, CA). Real-time quantitative PCR was performed in duplicate using SYBRGreen PCR core reagents kit (Applied Biosystems, Foster City, CA) with an Opticon-II thermocycler (Biorad, Hercules, CA). The expression of ISGs including myxoma resistance protein-1 (MX1; which encodes the protein MxA), lymphocyte antigen 6 complex locus E (Ly6E), and IFN-induced protein-44 (IFI44) was normalized to the expression of β -actin and the fold expression (normalized to the sample with the lowest expression) was calculated using the $2^{-\Delta\Delta C_t}$ method. Primers used in this study were: β -actin (forward) 5'-TCCCTGGAGAAGAGCTACGA-3', (reverse) 5'-AGCACTGTGTTGGCGTACAG-3'; MX1 (forward) 5'-CACGAAGAGGCAGCGGGATCG-3', (reverse) 5'-CCTTGCTCTCCACTTATCTTC-3'; IFI44 (forward) 5'-CTGGGGCTGAGTGAGAAAGA-3', (reverse) 5'-AGCGATGGGGAATCAATGTA-3'; and Ly6E (forward) 5'-AGGCTGCTTTGTTTGTGAC-3', (reverse) 5'-AGCAGGAGAAGCACATCAGC-3'.

Composite IFN-score calculation

As described in previous studies (Feng et al., 2006; Kirou et al., 2005), the mean and standard deviation of ISG expression was first calculated for the control group. For each patient, an expression score for each ISG was calculated based on the number of standard deviations above or below the mean expression of a control group. Complementary DNA from twenty healthy female volunteers (see above) served as controls in this study. A negative score indicates that the levels of ISG expression are below that of the mean of the control group (i.e. a score of -1 represents 1 standard deviation below the mean of the control group). A composite IFN score was determined for each patient based on the average of the three individual ISG scores (Feng et al., 2006). The 95th percentile of IFN score in the control group was used as a cutoff for determining whether a patient had high or normal

levels of ISG expression. Thus, a composite IFN score greater than 2 (equivalent to an average of two standard deviations above the mean expression levels in healthy controls for all three ISGs) was considered abnormally elevated. For group analysis, all patients with an IFN score ≥ 2 were classified in the IFN^{hi} group (n = 38) while those with a score < 2 comprised the IFN^{low} group (n = 20).

Longitudinal Analysis

For longitudinal analysis, neuropsychiatric questionnaires and peripheral blood ISG expression data were collected from 22 patients with multiple clinic visits during the study period. A total of 34 return visits were analyzed (12 patients with 1 return visit, 8 patients with 2 return visits, and 2 patients with 3 return visits). All return visits were within 3 to 6 months of the previous visit. Differences in each variable were calculated by subtracting the values measured at the prior visit from the return visit (i.e. a positive difference indicates an increase since the last visit).

Statistical Analysis

For quantitative variables, differences between groups were analyzed by Mann-Whitney U test. Differences in categorical variables were determined using Fisher's exact test. Bivariate correlations were assessed using Spearman's correlation coefficient. Data were presented as median (interquartile range) as indicated. For a significance of 0.05 (two-sided), a minimum of 51 subjects were needed for this study based on 80% statistical power to detect a moderate correlation (r) of 0.4 between parameters of depression/fatigue and the IFN score. Step-wise multiple regression analysis was performed to identify predictors of depression. Logarithmic transformation was applied to non-normally distributed variables in multivariate analysis where β is the standardized regression coefficient. BDI score was designated the dependent variable and all parameters from Tables 1 and 2 were included in the analysis. For all analyses, a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 11; SPSS Inc, Chicago, IL), StudySize (version 2.0; CreoStat Inc, Sweden) and GraphPad Prism 4.0 (GraphPad Software, San Diego, CA).

3. Results

In this study, we assessed the relationship between depression, fatigue, and peripheral blood ISG expression in 58 SLE patients. Table 1 provides demographics, clinical characteristics, and medication usage of all participants. Forty-nine of the 58 patients were receiving treatment with corticosteroids, antimalarials, and/or cytotoxic medications. Five patients had historical manifestations of CNS lupus including two with psychosis and three with seizures.

Depression and fatigue in patients with SLE

Depression and fatigue were analyzed using the Beck Depression Inventory (BDI) and Multidimensional Fatigue Inventory (MFI), respectively. The median BDI score was 10.5 [IQR 3 – 18] (Table 2), indicating the presence of some level of depression in ~50% of the patients. Mild to moderate depression (BDI range 10–18) was reported by 19 patients (32.8%), while 11 patients (19%) experienced moderate to severe depression (BDI range 19 – 29). Two patients reported BDI scores above 30, suggesting the presence of severe depression.

The MFI is comprised of five categories: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (Smets et al., 1995). The utility of this instrument has been validated in the U.S. adult population (Lin et al., 2009). Consistent with a previous study (Da Costa et al., 2006), SLE patients displayed greater levels of fatigue in all

categories compared to the general population. The highest median scores were found in general fatigue (15.5 [11.5 – 18]) and physical fatigue (13.5 [10.5 – 16]) while the lowest was found in reduced motivation (10.0 [7.5 – 13]; Table 2). The degree of fatigue as assessed by MFI was less than that in “chronic fatigued patients” but comparable to that in the “radiotherapy patients” used to validate the MFI (Smets et al. 1995). Depression and fatigue, as well as the levels of anxiety and pain were also evaluated by a visual analogue scale (Table 2).

The levels of depression (indicated by the BDI score) correlated strongly with all dimensions of fatigue measured by the MFI (Table 3). A similar association was found between depression and fatigue evaluated using the VAS ($r = 0.60$, $p < 0.0001$; data not shown). In addition, the levels of anxiety and pain (VAS) also were correlated with depression and fatigue measurements (Table 3). The prevalence of these neuropsychiatric manifestations was not associated with clinical parameters including SLE disease activity index (SLEDAI) scores, organ-specific manifestations (i.e. renal, skin, CNS), ACR criteria count, complement levels, or the profile of autoantibodies (anti-Sm, anti-dsDNA, anti-phospholipid; $p > 0.05$ for all comparisons; Table 3 and data not shown). Patients treated with antidepressants showed increased levels of physical fatigue while usage of opiate analgesics was associated with greater levels of depression, general fatigue and physical fatigue (Supplemental Table 1). The subgroup of SLE patients treated with opiate analgesics reported higher BDI scores while patients receiving either antidepressants or opiate analgesics exhibited slightly lower levels of physical fatigue. In contrast, usage of conventional lupus medications including corticosteroids, anti-malarials, and cytotoxics was not linked to the neuropsychiatric manifestations. Indeed, among the variables included in this study, only physical fatigue, reduced motivation and the use of opiate analgesics were identified as independent predictors of depression using a step-wise multiple regression analysis (data not shown).

Increased ISG expression in SLE patients

Recent studies have demonstrated that abnormal IFN-I production is associated with clinical features of SLE (Feng et al., 2006; Kirou et al., 2005; Zhuang et al., 2005). Accurate quantification of serum IFN-I levels by standard antibody-based assays is hindered by the presence of multiple IFN-I subtypes (i.e. at least 13 IFN- α species and a single IFN- β). This problem is further compounded by the prevalence of rheumatoid factor in sera from patients with autoimmune diseases, which binds antibodies in a non-specific manner and yields false-positive results. Because all IFN-I subtypes bind to a common receptor complex and activate the transcription of ISGs, quantification of ISG expression is a widely accepted surrogate readout of serum IFN-I levels that circumvents the flaws of direct IFN-I measurement. Increased ISG expression (represented either by individual ISGs or more accurately by a composite score derived from multiple ISGs) correlates with low complement levels, disease activity, renal involvement, and the production of specific autoantibodies (Baechler et al., 2003; Bennett et al., 2003; Feng et al., 2006; Kirou et al., 2005; Zhuang et al., 2005).

To examine whether depression and fatigue are linked to abnormal IFN-I levels, peripheral blood was obtained from each subject and the mRNA expression of three well-established ISGs: myxoma resistance protein-1 (MX1), IFN-inducible transcript 44 (IFI44), and lymphocyte antigen 6 complex locus E (Ly6E), were quantified by Q-PCR. Previous studies have demonstrated the utility and specificity of these ISGs in the assessment of IFN-I dysregulation in SLE patients (Feng et al., 2006; Kirou et al., 2005; Zhuang et al., 2005). A composite IFN score reflecting the ISG expression level in each patient's peripheral blood mononuclear cells vs. the mean expression in 20 healthy controls was calculated and used to

classify patients with normal (IFN^{low}) or elevated IFN-I (IFN^{hi}) levels (see Methods section).

Consistent with previous studies, about two-thirds of SLE patients displayed abnormally high expression of ISGs compared to healthy volunteers (Figure 1A–C). Accordingly, SLE patients exhibited significantly elevated composite IFN scores (4.61 [−0.10 – 12.7] vs. −.029 [−0.58 – 0.48], $p < 0.001$; Figure 1D). As expected, the expression of each ISG correlated highly with the composite IFN score and with one another ($p < 0.0001$ for all comparisons, Spearman's correlation). Elevated composite IFN scores in SLE patients also were associated with higher SLEDAI scores and the presence of anti-dsDNA and anti-Sm autoantibodies as reported in the past [(Kirou et al., 2005; Zhuang et al., 2005); Table 4 and data not shown]. Consistent with our previous observations (Zhuang et al., 2005), the composite IFN scores were not affected by the usage of medications including corticosteroids, antimalarials, and cytotoxics (Supplemental Table 1).

Endogenous IFN-I levels are not correlated with depression and fatigue

When patients were divided into groups with normal (IFN^{low}; $n = 20$) or elevated IFN scores (IFN^{high}; $n = 38$) based on the comparison to normal healthy controls, we found no difference in the levels of depression (BDI), general fatigue (MFI) or physical fatigue (MFI) between the two groups (Figure 2A). Other dimensions of MFI and VAS scores were similarly no different ($p > 0.05$ for all comparisons; data not shown). Indeed, bivariate analysis revealed that neither the composite IFN scores nor individual ISG expression levels were associated with BDI, MFI or VAS variables (Table 4).

Since IFN-I levels can fluctuate during the course of disease (unpublished observation), a longitudinal study was conducted in a subset of patients ($n = 22$) with one or more return clinic visits during the study period to follow the changes in ISG expression and neuropsychiatric manifestations. While the levels of depression and fatigue fluctuated between clinic visits in many patients, these alterations were not correlated with the changes in the composite IFN score (Figure 2B). Changes in other components of MFI and VAS parameters also were not associated with alterations in the IFN score ($p > 0.05$ for all comparisons; data not shown). Therefore, the lack of an association between abnormal IFN-I levels and the extent of depression and fatigue in SLE patients was supported by both cross-sectional and longitudinal analysis.

4. Discussion

Despite the high prevalence of depression and fatigue among patients with SLE, the cause of these manifestations remains unclear. A number of recent studies suggest that IFN-I play a key role in the pathogenesis of SLE. Elevated serum IFN-I levels as reflected by increased ISG expression correlate with disease severity, renal manifestations, autoantibody production, and endothelial dysfunction (Feng et al., 2006; Kirou et al., 2005; Lee et al., 2007). Because depression and fatigue are common complications of recombinant IFN-I therapy (Dieperink et al., 2000; McHutchison et al., 1998), we investigated whether excess endogenously produced IFN-I contributes to these neuropsychiatric findings in lupus patients. Both cross-sectional and longitudinal analysis demonstrated that increased ISG expression levels are not associated with the severity of depression or fatigue.

The degree of depression and fatigue in SLE patients reported here is comparable to previous studies. Consistent with other investigations that employed the BDI for depression screening (Iverson et al., 2001; Jump et al., 2005), our study shows that about half of SLE patients experience some level of depression, usually in the mild to moderate range. The profile of fatigue dimensions assessed by the MFI also is comparable to that from a larger

cohort recently reported by Da Costa et al. (Da Costa et al., 2006). That study and the present one both demonstrate the predominance of general fatigue and physical fatigue in patients with SLE. However, while depression and fatigue levels were highly correlated, neither was related to disease manifestations, serologic measurements or usage of most medications analyzed in this study. The observation of increased BDI and MFI scores associated with opiate analgesic usage (data not shown) is likely explained by the physical and emotional impact of chronic pain in that subset of patients.

In line with these findings, depression and fatigue associated with SLE are independent of disease activity determined by established indices [e.g. SLE disease activity index (SLEDAI)] and serological indicators in past studies (Gladman et al., 1996; Jump et al., 2005; Shortall et al., 1995; Wang et al., 1998). Interestingly, coping skills and perceived social support are better predictors of depression and fatigue (Jump et al., 2005; Shortall et al., 1995), illustrating the impact of social factors that may be overlooked in chronic diseases. It is noteworthy that autoantibodies against N-methyl-D-aspartate receptor (anti-NR2) and ribosomal P proteins (anti-P) in lupus patients have been linked to the development of cognitive dysfunction and depression (Lapteva et al., 2006; Omdal et al., 2005; Schneebaum et al., 1991). However, the association is somewhat controversial and further work is required to understand the role of these autoantibodies (Eber et al., 2005; Harrison et al., 2006; Teh et al., 1992). In the current study we did not test for anti-NR2 antibodies and only 3 of the 58 patients were anti-P positive.

In view of the ability of IFN- α to trigger neuropsychiatric side effects, several factors may contribute to the lack of association between elevated IFN levels and the severity of depression and fatigue in lupus patients. First, while endogenous IFN-I production is elevated in SLE patients compared to healthy individuals, it is possible that greater serum levels than those seen in SLE are required to trigger neuropsychiatric manifestations. The kinetics of the increased IFN-I levels also may be important as patients receiving weekly or biweekly infusions of recombinant IFN-I may display greater fluctuations of serum IFN-I levels than lupus patients. Detailed studies on the levels of IFN-I and expression of ISGs following IFN-I therapy are required to address these issues. However, in a previous study of hepatitis C patients treated with IFN- α , MX1 expression exhibited a median mRNA level ~10 fold higher than baseline (Gilli et al., 2002). Baseline values in HCV patients were only slightly higher than in normal controls. The MX1 expression levels seen 12 hours after administration of exogenous IFN- α (Gilli et al., 2002) was comparable to that seen chronically in many SLE patients (Figure 1A), suggesting that differences in the peak IFN-I levels may not explain the present data.

The mechanism responsible for the development of neuropsychiatric manifestations following IFN- α therapy remains unclear and it is not certain why exogenous, but not endogenous, IFN-I is associated with depression. Perhaps IFN-I levels in the CNS, rather than in the peripheral blood, are critical for the development of depression and fatigue. An association between IFN- α levels in the cerebrospinal fluid (CSF) and lupus psychosis has been suggested (Shiozawa et al., 1992). However, in another study increased levels of IFN- α in the CSF from SLE patients did not correlate neuropsychiatric symptoms (Jonsen et al., 2003). In patients with hepatitis C, IFN- α administered subcutaneously was shown to penetrate the blood brain barrier and the levels of IFN- α in the CSF reached approximately 1% of the serum concentration (Raison et al., 2009a). The CSF levels of IFN- α did not correlate with depressive symptoms. It remains possible that IFN-inducible factors, instead of IFN- α , are responsible for the neuropsychiatric side effects. IFN- α therapy is associated with elevated CSF levels of interleukin-6 (IL-6), which correlates with reduced levels of the serotonin metabolite 5-hydroxyindoleacetic acid (Raison et al., 2009a). CSF levels of IL-6 are also elevated in lupus patients with neuropsychiatric manifestations but the relationship

between IL-6 and IFN-I activity has not been examined (Fragoso-Loyo et al., 2007). Moreover, mood symptoms associated with IFN- α therapy could be due to tryptophan depletion secondary to the IFN-I mediated activation of indoleamine 2,3-dioxygenase (IDO), an enzyme that converts L-tryptophan to the neuroactive metabolites L-kynurenine and quinolinic acid (Capuron et al., 2003; Capuron et al., 2002). CSF levels of L-kynurenine and quinolinic acid are increased following IFN- α therapy and correlate with the levels of depression (Raison et al., 2009b). Increased IDO activity and elevated serum levels of L-kynurenine are reported in lupus patients (Pertovaara et al., 2007; Widner et al., 2000), although a connection with neuropsychiatric manifestations has not been established. Additional studies in these areas are needed to determine how exogenous interferon precipitates depressive illness and why IFN-I overproduction in SLE is not associated with mood manifestations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Increased ISG expression in patients with SLE

A-C) Comparison of peripheral blood expression of mRNA for three ISGs (IFI44, Ly6E, and MX1) between SLE patients (n = 58) and healthy controls (n = 20). **D)** Comparison of composite IFN scores between SLE patients and healthy controls. The composite score represents the average number of standard deviations (from all three individual ISGs) from the mean of the control group. Dashed line indicates the cut-off for two standard deviations above the mean of healthy controls. For all panels, p values were computed using the Mann-Whitney U test. Solid line represents the median.

Figure 2. Depression and fatigue in patients with SLE are not associated with increased levels of IFN-I

A) Comparison of the levels of depression (BDI), general fatigue (MFI) and physical fatigue (MFI) in SLE patients with a normal (IFN^{low} group; n = 20) or elevated (IFN^{high} group; n = 38) composite IFN score. p values were computed using Mann-Whitney's U test. Solid line represents the median. **B)** Correlation between changes in the composite IFN score and changes in depression, general fatigue, and physical fatigue from longitudinal analysis of 34 return clinic visits by 22 SLE patients. Rho and p values were calculated using Spearman's correlation.

Table 1**Demographics and Clinical Characteristics**

	SLE (n = 58)	NHC (n = 20)
Female, no. (%)	55 (94.8%)	17 (85%)
Age, mean (range)	39.6 (21 – 66)	37.8 (23 – 61)
Race, no. (%)		
African-American	17 (29.3%)	8 (40.0%)
White	25 (43.1%)	7 (35.0%)
Others	16 (27.6%)	5 (25.0%)
<i>Serum measurements</i>		
C3 (mg/dL), mean $\pm$ sd	99.1 $\pm$ 30.1	121.6 $\pm$ 21.7
C4 (mg/dL), mean $\pm$ sd	18.5 $\pm$ 10.2	24.7 $\pm$ 7.0
<i>SLE manifestations</i>		
SLEDAI, mean (range)	3.1 (0 – 17)	-
Disease duration (yrs), mean (range)	11.7 (1 – 43)	-
ACR Criteria, mean (range)	5.8 (4 – 9)	-
Positive ANA, no. (%)	58 (100%)	-
Lupus Nephritis, no. (%)	31 (53.4%)	-
Seizures, no. (%)	3 (5.2%)	-
Psychosis, no. (%)	2 (3.4%)	-
Anti-dsDNA, no. (%)	41 (70.7%)	-
Anti-Sm, no. (%)	28 (48.3%)	-
Anti-phospholipid, no. (%)	30 (51.7%)	-
<i>Medication usage, number (%)</i>		
NSAIDs	25 (43.1%)	-
Antimalarials	29 (50%)	-
Antidepressants	14 (24.1%)	-
Anxiolytics	7 (12.1%)	-
Cytotoxics	26 (44.83%)	-
Corticosteroids	42 (72.4%)	-
Hypnotics	10 (17.2%)	-
Thyroid replacement	10 (17.2%)	-
Anticonvulsants	9 (15.5%)	-
Opiate analgesics	17 (29.3%)	-
Muscle relaxants	5 (8.6%)	-

Abbreviations: SLE, systemic lupus erythematosus; NHC, normal healthy controls; SLEDAI, SLE disease activity index; ACR, American College of Rheumatology; ANA, antinuclear antibodies; sd, standard deviation.

Table 2

Evaluation of depression and fatigue in patients with SLE

	Range	Minimum	Maximum	Median (IQR)
BDI	0 – 63	0	31	10.5 (3 – 18)
General Fatigue, MFI ^a	4 – 20	4	20	15.5 (11.5 – 18)
Physical Fatigue, MFI	4 – 20	4	20	13.5 (10.5 – 16)
Reduced Activity, MFI	4 – 20	4	20	11.5 (7 – 14)
Reduced Motivation, MFI	4 – 20	4	18	10 (7.5 – 13)
Mental Fatigue, MFI	4 – 20	4	20	12 (7 – 15)
Fatigue VAS	0 – 100	0	100	65 (19.5 – 83.5)
Anxiety VAS	0 – 100	0	100	21 (1 – 57.5)
Depression VAS	0 – 100	0	97	13 (1 – 49.5)
Energy VAS	0 – 100	0	100	40 (16 – 69)
Pain VAS	0 – 100	0	96	31 (3 – 62)

Abbreviations: IQR, interquartile range; BDI, Beck's depression index; MFI, multidimensional fatigue index; VAS, visual analogue scale.

^aBased on a recent study (Lin et al., 2009), the median and IQR for MFI measurements in healthy U.S. adults are: general fatigue, 8 (6 – 11); physical fatigue, 7 (5 – 10); reduced activity, 8 (6 – 12); reduced motivation, 6 (4 – 8); and mental fatigue, 7 (4 – 9).

Table 3

Coefficient of correlation for bivariate analysis of neuropsychiatric parameters

	Physical Fatigue	Reduced Activity	Reduced Motivation	Mental Fatigue	Anxiety	Pain	BDI	SLEDAI
General Fatigue	$b_{0.712}$	$b_{0.506}$	$b_{0.665}$	$b_{0.671}$	$b_{0.405}$	$b_{0.510}$	$b_{0.690}$	-0.117
Physical Fatigue	-	$b_{0.705}$	$b_{0.581}$	$b_{0.612}$	$b_{0.467}$	$b_{0.625}$	$b_{0.725}$	-0.098
Reduced Activity	-	-	$b_{0.681}$	$b_{0.499}$	$b_{0.466}$	$b_{0.657}$	$b_{0.625}$	-0.188
Reduced Motivation	-	-	-	$b_{0.596}$	$b_{0.422}$	$b_{0.613}$	$b_{0.595}$	-0.230
Mental	-	-	-	-	$b_{0.358}$	$b_{0.454}$	$b_{0.654}$	-0.253
Fatigue Anxiety	-	-	-	-	-	$b_{0.510}$	$b_{0.606}$	-0.100
Pain	-	-	-	-	-	-	$b_{0.625}$	-0.049
BDI	-	-	-	-	-	-	-	-0.019

^a $p < 0.01$

^b $p < 0.001$ (Spearman's correlation test)

Table 4

Coefficient of correlation from bivariate analysis of ISG expression and neuropsychiatric parameters^a

	General Fatigue	Physical Fatigue	Reduced Activity	Reduced Motivation	Mental Fatigue	Anxiety	Pain	BDI	SLEDAI
IFN Score	-0.142	-0.130	0.020	-0.149	-0.204	-0.133	-0.071	-0.178	0.330 ^a
MX1	-0.149	-0.088	0.014	-0.135	-0.105	-0.133	-0.038	-0.140	0.285 ^a
IFI44	-0.095	-0.093	0.115	-0.080	-0.160	-0.047	0.025	-0.079	0.427 ^b
Ly6E	-0.154	-0.130	-0.003	-0.169	-0.218	-0.117	-0.082	-0.221	0.222

^a p < 0.05

^b p < 0.01 (Spearman's correlation test)